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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/403,980	01/19/2000	ERIC VIVIER	1721-18	7917

7590 02/25/2003

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EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/403,980	VIVIER ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *13,14,17-20,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 15, 16, 21, 24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparisons A-D* .

DETAILED ACTION

1. Formal Matters

A. The Information Disclosure Statement, filed 10/2/00, has been entered into the record.

B. Claims 1-25 are pending in the application and were subject to restriction in Paper No. 14, mailed 10/30/02. In Paper No. 15, filed 12/2/02, Applicants elected Group I, claims 1-12, 15, 16, 21 and 24-25. Claims 13, 14, 17-20, 22 and 23 are withdrawn as being drawn to non-elected non-elected subject matter. Therefore, claims 1-12, 15, 16, 21 and 24-25 are the subject of this Office Action.

2. Specification

A. The specification is objected to since the first line of the specification does not reference priority to PCT/FR98/00883.

B. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

3. Claim Objections

A. Claims 1-12, 21, 24 and 25 are objected to since these claims should begin with the appropriate article, for example, "A," "An," or "The."

B. Claim 1 is objected to since the sequence of the ITAM molecule must be accompanied by a sequence identifier since it contains four or more amino acids. See MPEP 2421.02 and 2422 (37 CFR 1.821(a).

C. Claims 7 and 16 are objected to since they recite non-elected SEQ ID NOs in the claims.

D. Claim 24 is objected to since the phrase "adaptor carryout" is not clear.

4. Claim Rejections - 35 USC § 112, first paragraph – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 1-12, 15, 16, 21, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2 and 28, does not reasonably provide enablement for polypeptides encoding fragments and homologs of any KARAP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

First, the breadth of the claims is excessive with regard to claiming "**all KARAPs**," "**fragments**" or "**homologs**" thereof, as well as their encoding nucleic acid molecules, as well as proteins which are "**modified to inhibit their signal transduction capabilities**." These modified proteins, fragments and homologs would have one or more amino acid substitutions, deletions, insertions and/or additions to the KARAP disclosed in the specification, SEQ ID NO:2 and 28. Similarly, the encoding nucleic acids and their "**variants**" would have one or more nucleotide substitutions, deletions, insertions and/or additions to the nucleic acid molecules encoding the KARAP disclosed in the specification. Applicants only identify two KARAPs, SEQ ID NO:2 and 28, but provide no other guidance or working examples of these, or any other KARAPs. Applicants state in the specification (page 7, lines 1-4) that other KARAPs are essentially constituted by SEQ ID NO:11-15 and 17, which are, or involve, the consensus sequence of a known KARAP. Therefore, it is not clear if SEQ ID NO:11-15 and 17 are in fact full-length KARAPs. SEQ ID NO:2 is 87 residues, whereas SEQ ID NO:11-15, 17 and 28 range from 111 to 160 residues. Applicants have not taught which amino acid residues for any of SEQ ID NO:2, 11-15, 17 and 28 are required in order to maintain the structural and functional characteristics of a native KARAP (e.g. "transducing a signal orienting from KAR"), or which residues could be modified to inhibit signal transduction, other than addition of a phosphonate group, or replacing the tyrosine. Furthermore, it is not predictable to one of ordinary skill in the art what the functions of these proteins, or encoding nucleic acid molecules, are, or what residues to change to inhibit protein function.

Regarding claim 2, Applicants are attempting to obtain any polypeptide from any species which is obtained by the claimed process. Again, Applicants have only provided minimal guidance and working examples of two KARAPs found in mice (SEQ ID NO:2 and 28). Applicants have provided no guidance or working examples of KARAPS other than SEQ ID NO:2 and 28, or in species other than mouse, nor have they provided any guidance or working examples of "fragments" of these proteins, including that of SEQ ID NO:2, or "homologs" of any KARAP other than SEQ ID NO:2 and 28. Again, Applicants have not taught which amino acid residues for any KARAP are required in order to maintain its structural and functional characteristics, nor is it predictable to one of ordinary skill in the art what the functions of these nucleic acids, or the proteins which they encode, are.

Furthermore, claim 21 recites "**pharmaceutical composition**," but Applicants have provided no guidance or working examples of any methods of treatment for any diseases using these proteins, including any data or treatment regimen. Furthermore, it is not predictable to one of ordinary skill in the art how to use a pharmaceutical composition, given this lack of guidance and working examples. In addition, the use of nucleic acids is considered gene therapy and should be deleted from the claim, or else

the claim will be restricted in the next Office Action. Gene therapy is separate subject matter from the use of proteins. Applicants can overcome the part of the rejection by amending claim 21 to recite the proteins which are "in an inert carrier."

In summary, the breadth of the claims is excessive with regard to Applicants claiming all KARAPs, "fragments" or "homologs" thereof, including any polypeptide from any species which is obtained by the process of claim 2, as well as their encoding nucleic acids and "variants." There is also a lack of guidance and working examples of these proteins and pharmaceutical compositions comprising them. Applicants have not taught which amino acid residues for any KARAP are required in order to maintain the structural and functional characteristics of a native KARAP (e.g. "transducing a signal orienting from KAR"). These factors, along with the lack of predictability to one of ordinary skill in the art as to what the functions of these proteins are leads the Examiner to hold that undue experimentation is necessary to practice the invention as claimed.

5. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 1-12, 15, 16, 21, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These are genus claims. These protein "**fragments**" and "**homologs,**" as well as proteins which are "**modified to inhibit their signal transduction capabilities**" would have one or more amino acid substitutions, deletions, insertions and/or additions to the KARAP disclosed in the specification, SEQ ID NO:2 and 28. Similarly, the encoding nucleic acids and "**variants**" would have one or more nucleotide substitutions, deletions, insertions and/or additions to the nucleic acid molecules encoding the KARAP disclosed in the specification. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. The requirements of claims 1 and 2 are broad. Thus the scope of the claims, including claim 10, includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acid or protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or

characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO:2 and 28, or their encoding nucleic acids, alone are insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus.

The specification provides a written description of only a small number of these protein constructs (SEQ ID NO:2 and 28). No other species are described, or structurally contemplated, within the instant specification. Therefore, one skilled in the art cannot reasonably visualize or predict critical nucleic acid residues which would structurally characterize the genus of nucleic acids encoding the genus of KARAP proteins claimed, because it is unknown and not described what structurally constitutes any different nucleic acids encoding KARAPs, or KARAPs, or their encoding nucleic acids from any different species, which are further not described, or any "homologs," "fragments," or "variants" thereof; thereby not meeting the written description requirement under 35 USC 112, first paragraph. Thus, Applicant was not in possession of the claimed genus at the time the invention was made.

6. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claim 1 is confusing since the term "10+2 and 16+2" is not understood.

B. Claim 3 recites the limitation "said cells." There is insufficient antecedent basis for this limitation in the claim.

C. Claim 24 is confusing since it is not a guarantee that a molecule which binds to a receptor can produce an activity on said receptor. In other words, binding does not necessarily lead to a function.

D. Claims 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a conclusion step stating the intended goal. For example, **and without adding new matter**, "wherein the binding of said candidate molecule demonstrates that said molecule activates KAR."

7. Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 1-9, 15, 16 and 21 are rejected under 35 U.S.C. 102(a) as being anticipated by Marra et al. (1997). The claims recite an isolated polypeptde which is able to restore deficient KAR activation which has the characteristics recited in claim 1, or is obtained by the method of claim 2. The polypeptide also binds a molecule having an SH2 or PTB binding domain, consist essentially of SEQ ID NO:2, and is capable of crossing a cell membrane. The claims also recite that the protein is phosphorylated, can form dimers and is found on NK or T cells. The nucleic acid must have a sequence consisting essentially of SEQ ID NO:1. Pharmaceutical compositions are also disclosed.

Marra et al. teach a polynucleotide which is 100% identical to that of SEQ ID NO:1 of the present invention (Sequence Comparison A) which encodes a protein which is 100% identical to that of SEQ ID NO:2 of the present invention (Sequence Comparison C). Since the nucleic acid and protein of Marra et al. are identical to those of the present invention, it would be inherent that these molecules (i.e. inherent in the protein structure) would have the properties and meet the limitations of the claims. The artisan would immediately envision the protein of Marra et al. in a pharmaceutical composition, such as water, or buffer, especially in the absence of any limitations that the composition be sterile.

Though not being used in the prior art rejection, but only to provide evidence of inherency, Blery et al. do teach the presence of that these proteins are phosphorylated and form dimers (page 8989, right column, first full paragraph through line 4 of the left column of page 8990).

B. Claims 1-3, 6, 7, 9, 10, 15, 16 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Marra et al. (1997). The claims recite an isolated polypeptde which is able to restore deficient KAR activation which has the characteristics recited in claim 1, or is obtained by the method of claim 2. The polypeptide also binds a molecule having an SH2 or PTB binding domain, consist essentially of SEQ ID NO:2 and is capable of crossing a cell membrane. The claims also recite that the protein is phosphorylated, can form dimers and is found on NK or T cells. The nucleic acid must have a sequence consisting essentially of SEQ ID NO:1. Pharmaceutical compositions are also disclosed.

Marra et al. teach a polynucleotide which is 79.3% identical to that of SEQ ID NO:1 of the present invention (Sequence Comparison B) which encodes a protein which is 99% identical to that of SEQ ID NO:2 of the present invention (Sequence Comparison D). Therefore, this nucleic acid would meet the limitations of the claims since it "essentially comprises SEQ ID NO:1." Since the protein of Marra et al. is 99% identical to that of the present invention, it would be inherent (i.e. inherent in the protein structure) that this protein would have the properties and meet the limitations of the claims. In addition, due to the amino acid differences, in absence of evidence to the contrary, this protein's capacity to transduce a signal may be inhibited. The artisan would immediately envision the protein of Marra et al. in a pharmaceutical composition, such as water, or buffer, especially in the absence of any limitations that the composition be sterile.

Though not being used in the prior art rejection, but only to provide evidence of inherency, Blery et al. do teach the presence of that these proteins are phosphorylated and form dimers (page 8989, right column, first full paragraph through line 4 of the left column of page 8990).

8. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 3, 4, 5, 21, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Marra et al. (1996) or Marra et al (1997) each in view of Blery et al. (J. Biol. Chem. 272(14):8989-8996, 1997). The teachings of both Marra et al. (1996) and (1997) are recited in the above rejection under 35 USC 102. The claims also recite that at least one tyrosine is phosphorylated, that it forms dimers, as well as methods for identifying molecules which modulate a KAP-related activity.

Neither Marra et al. (1996) nor Marra et al. (1997) teach that at least one tyrosine is phosphorylated, that it forms dimers, as well as methods for identifying molecules which modulate a KAP-related activity. However, Blery et al. do teach these limitations (page 8989, right column, first full paragraph through line 4 of the left column of page 8990; Figures 2, 3, and 5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Blery et al. by substituting a cDNA in the polycloning region of the

vector with the polynucleotide (cDNA) of either Marra et al. (1996) or Marra et al. (1997) for the purpose of transfecting a host cell as taught by Blery et al. since both of these nucleic acid molecules encode proteins which modulate KAR activation and the methods of Blery et al. could be used to study the function of the proteins of either Marra et al. (1996) or Marra et al. (1997).

One of ordinary skill in the art would have been motivated to make this substitution in order to express the protein encoded by the introduced DNA in a host cell to perform ligand binding and functional assays. There would have been a reasonable expectation of success for a person of ordinary skill in the art to make this invention since these techniques are widely used in the art and are highly successful. The present invention, therefore, is *prima facia* obvious over the above references in the absence of evidence to the contrary.

In addition, Blery et al. also teach the use of buffers ("Experimental Procedures"), which can be considered pharmaceutical compositions. Therefore, pharmaceutical compositions comprising the protein of both Marra et al. (1996) or Marra et al. (1997) would have been obvious.

B. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Marra et al. (1996) or Marra et al (1997) each in view of Burke et al. The teachings of both Marra et al. (1996) and Marra et al (1997) are recited in the above rejection under 35 USC 102. Neither Marra et al., nor Marra et al. teach the modification of a protein to inhibit its capacity to transduce a signal, including the addition of phosphonate groups, or the substitution of a tyrosine with a phenylalanine. However, Burke et al. do teach the production of a phosphonate and phenylalanine-substituted tyrosyl residues in a protein (see entire first page, including "scheme"). It would have been obvious to one of ordinary skill in the art at the time of the present invention to have substituted the phosphonate group and phenylalanine for a tyrosine in the protein of either Marra et al. (1996) or Marra et al (1997) since, according to Burke et al., as is well-known in the art, post-translational modification of tyrosyl residues in certain proteins by either removal or addition of phosphate groups is an important mechanism of signal transduction, providing a need to produce stabile analogs of these proteins to study their mechanisms of action as well as for potential therapeutics. Therefore, the artisan would have been motivated to have substituted phosphonate groups and/or phenylalanine substituted mutants from the proteins of either Marra et al. (1996) or Marra et al (1997) since these proteins were known to have tyrosyl residues. Therefore, these modifications would have allowed for further characterization of the proteins.

9. Conclusion

A. It is brought to Applicants' attention that, due to the content, limitations and overall complexity of claim 2, it cannot be properly searched for prior art. Therefore, it is believed that any protein which meets the limitation of claim 1 will also meet the limitation of claim 2, in absence of evidence to the contrary.

B. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
February 24, 2003